3.0 NON-TECHNICAL ABSTRACT

Melanoma is a common and frequently fatal skin cancer. Approximately 47,000 cases of cutaneous melanoma were diagnosed in the U.S. in 2000. About two-thirds of patients can be cured by surgery. Others, however, either are not candidates for surgery or have their melanoma come back after surgery. There are no ways to cure such patients and most will ultimately die from their melanoma.

Melanoma sometimes responds to the body's immune defense system, which is active against invading pathogens and some cancers. Researchers have looked for ways to boost the immune system to take advantage of this for people with melanoma who are not cured by surgery. The body makes molecules termed cytokines that help activate its built-in defenses. One of these, interleukin-2 (IL-2), can be given intravenously as a protein drug. It is often used for people with melanoma who cannot be cured by surgery but only gives responses 17% of the time. Most people still experience relapse and die from their melanoma. This treatment is also uncomfortable for many patients and has risks of side effects in the lung, heart and kidney. In addition to IL-2, other cytokine proteins made by the body that stimulate immune defenses include interferons and another interleukin, IL-12. As with IL-2, attempts to treat cancers including melanoma with molecules like these have been only partially successful and have demonstrated significant side effects.

All the body's functions, including the production of cytokine proteins, are controlled by genes encoded by cells' DNA. Some of the problems associated with giving therapeutic cytokine protein intravenously may be avoided by instead delivering the gene that directs production of the protein. Transferring the DNA that encodes the desired cytokine protein directly into the tumor against which immune attack is desired can result in local production of molecules that will stimulate an immune response against the tumor. In this way, some of the body-wide side effects might be avoided while the immune stimulatory benefits may be retained. When used to deliver the genes for an interferon termed IFN-a and for the cytokine IL- 12, this approach has shown promise in experimental systems.

A clinical trial has been designed which aims to evaluate the safety of this approach in patients. First, gradually increasing amounts of DNA encoding IFN-a and IL- 12 plus a stabilizing agent, up to a pre-determined limit, will be injected into accessible tumors of patients who have cancer not curable by surgery. Once the maximum dose that can be safely tolerated by patients is determined, additional patients with incurable melanoma will be treated at that dose. The anti-tumor effects of the approach will be assessed in the fraction of patients that have significant shrinkage of their melanoma tumors.